**Docket No.: PF-0505-2 DIV**

Certificate of Mailing

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: ~~Box Non-Fee Amendment~~ Commissioner for Patents, Washington, D.C. 20231 on November 18, 2002.

By: Rick Ekstrom Printed: Rick Ekstrom

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of: Hillman et al.

| | | | |
|---|---|---|---|
| Title: | GROWTH ASSOCIATED PROTEASE INHIBITOR HEAVY CHAIN PRECURSOR | | |
| Serial No.: | 09/828,423 | Filing Date: | April 05, 2001 |
| Examiner: | Decloux, A. | Group Art Unit: | 1644 |



Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF LARS MICHAEL FURNESS
UNDER 37 C.F.R. § 1.132

I, L. MICHAEL FURNESS, a citizen of the United Kingdom, residing at 2 Brookside, Exning, Newmarket, United Kingdom, declare that:

1. I was employed by Incyte Genomics, Inc. (hereinafter "Incyte") as a Director of Pharmacogenomics until December 31, 2001. I am currently under contract to be a Consultant to Incyte Genomics, Inc.

2. In 1984, I received a B.Sc.(Hons) in Biomolecular Science (Biophysics and Biochemistry) from Portsmouth Polytechnic.

From 1985-1987 I was at the School of Pharmacy in London, United Kingdom, during which time I analyzed lipid methyltransferase enzymes using a variety of protein analysis methods, including one-dimensional (1D) and two-dimensional (2D) gel electrophoresis, HPLC, and a variety of enzymatic assay systems.

I then worked in the Protein Structure group at the National Institute for Medical Research until 1989, setting up core facilities for nucleic acid synthesis and sequencing, as well as assisting in programs on protein kinase C inhibitors.

After a year at Perkin Elmer-Applied Biosystems as a technical specialist, I worked at the Imperial Cancer Research Fund between 1990-1992, on a Eureka-funded program collaborating with Amersham Pharmacia in the United Kingdom and CEPH (Centre d'Etude du Polymorphisme Humaine) in Paris, France, to develop novel nucleic acid purification and characterization methods.

In 1992, I moved to Pfizer Central Research in the United Kingdom, where I stayed until 1998, initially setting up core DNA sequencing and then a DNA arraying facility for gene expression analysis in 1993. My work also included bioinformatics and I was responsible for the support of all Pfizer neuroscience programs in the United Kingdom. This then led me into carrying out detailed bioinformatics and wet lab work on the sodium channels, including antibody generation, Western and Northern analyses, PCR, tissue distribution studies, and sequence analyses on novel sequences identified.

In1998 I moved to Incyte Genomics, Inc., in the Pharmacogenomics group, looking at the application of genomics and proteomics to the pharmaceutical industry. In 1999 I was appointed director of the LifeExpress Lead Program which used microarray and protein expression data to identify pharmacologically and toxicologically relevant mechanisms to assist in improved drug design and development.

On December 12, 2001 I founded Nuomics Consulting Ltd., in Exning, U.K., and I am currently employed as Managing Director. Nuomics Consulting Ltd. will be providing expert technical knowledge and advice to businesses around the areas of genomics, proteomics, pharmacogenomics, toxicogenomics and chemogenomics.

3. I have reviewed the specification of a United States patent application of Serial No. 09/828,423, that I understand was filed on April 5, 2001 in the names of Jennifer Hillman et al. (hereinafter "Hillman '423 application"). Furthermore, I understand that this U.S. patent application was a divisional application of and claimed priority to U.S. application Serial No. 09/388,774 filed September 2, 1999 (herein after "the Hillman '774 application), now U.S.

Patent No. 6,228,991, which in turn was a divisional application of and claimed priority to U.S. application Serial No. 09/074,579 filed May 7, 1998 (hereinafter "the Hillman '579 application"), now U.S. Patent No. 6,001,596, all having the identical specification, with the exception of corrected typographical errors and reformatting. Thus page and line numbers may not match as between the Hillman '423 application and the Hillman '579 application. My remarks herein will therefore be directed to the Hillman '579 application, and May 7, 1998, as the relevant date of filing. In broad overview, the Hillman '579 specification pertains to certain nucleotide and amino acid sequences and their use in a number of applications, including gene and protein expression monitoring applications that are useful in connection with (a) developing drugs (e.g., for the treatment of cancer), and (b) monitoring the activity of drugs for purposes relating to evaluating their efficacy and toxicity.

4. I understand that (a) the Hillman '423 application contains claims that are directed to an isolated antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:1 (hereinafter "the SEQ ID NO:1 polypeptide"), and (b) the Patent Examiner has rejected those claims on the grounds that the specification of the Hillman '423 application allegedly does not disclose a substantial, specific and credible utility for the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds. I further understand that whether or not a patent specification discloses a substantial, specific and credible utility for its claimed subject matter is properly determined from the perspective of a person skilled in the art to which the specification pertains at the time of the patent application was filed. In addition, I understand that a substantial, specific and credible utility under the patent laws must be a "real-world" utility.

5. I have been asked (a) to consider with a view to reaching a conclusion (or conclusions) as to whether or not I agree with the Patent Examiner's position that the Hillman '423 application and its parent, the Hillman '579 application, allegedly does not disclose a substantial, specific and credible "real-world" utility for the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds, and (b) to state and explain the bases for any conclusions I reach. I have been informed that, in connection with my

considerations, I should determine whether or not a person skilled in the art to which the Hillman '579 application pertains on May 7, 1998, would have concluded that the Hillman '579 application disclosed, for the benefit of the public, a specific beneficial use of the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds in their then available and disclosed form. I have also been informed that, with respect to the "real-world" utility requirement, the Patent and Trademark Office instructs its Patent Examiners in Section 2107 of the Manual of Patent Examining Procedure, under the heading "I. 'Real-World Value' Requirement":

> "Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact 'useful' in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified utility and inventions whose specific utility requires further research to identify or reasonably confirm."

6. I have considered the matters set forth in paragraph 5 of this Declaration and have concluded that, contrary to the position I understand the Patent Examiner has taken, the specification of the Hillman '579 application disclosed to a person skilled in the art at the time of its filing a number of substantial, specific and credible real-world utilities for the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds. More specifically, persons skilled in the art on May 7, 1998 would have understood the Hillman '579 application to disclose the use of claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds as research tools in a number of gene and protein expression monitoring applications that were well-known at that time to be useful in connection with the development of drugs and the monitoring of the activity of such drugs. I explain the bases for reaching my conclusion in this regard in paragraphs 7-13 below.

7. In reaching the conclusion stated in paragraph 6 of this Declaration, I considered (a) the specification of the Hillman '579 application, and (b) a number of published articles and patent documents that evidence gene and protein expression monitoring techniques

that were well-known before the May 7, 1998 filing date of the Hillman '579 application. The published articles and patent documents I considered are:

(a) Anderson, N.L., Esquer-Blasco, R., Hofmann, J.-P., Anderson, N.G., A Two-Dimensional Gel Database of Rat Liver Proteins Useful in Gene Regulation and Drug Effects Studies, Electrophoresis, 12, 907-930 (1991) (hereinafter "the Anderson 1991 article") (copy annexed at Tab A);

(b) Anderson, N.L., Esquer-Blasco, R., Hofmann, J.-P., Mehues, L., Raymackers, J., Steiner, S. Witzmann, F., Anderson, N.G., An Updated Two-Dimensional Gel Database of Rat Liver Proteins Useful in Gene Regulation and Drug Effect Studies, Electrophoresis, 16, 1977-1981 (1995) (hereinafter "the Anderson 1995 article") (copy annexed at Tab B);

(c) Wilkins, M.R., Sanchez, J.-C., Gooley, A.A., Appel, R.D., Humphery-Smith, I., Hochstrasser, D.F., Williams, K.L., Progress with Proteome Projects: Why all Proteins Expressed by a Genome Should be Identified and How To Do It, Biotechnology and Genetic Engineering Reviews, 13, 19-50 (1995) (hereinafter "the Wilkins article") (copy annexed at Tab C);

(d) Celis, J.E., Rasmussen, H.H., Leffers, H., Madsen, P., Honore, B., Gesser, B., Dejgaard, K., Vandekerckhove, J., Human Cellular Protein Patterns and their Link to Genome DNA Sequence Data: Usefulness of Two-Dimensional Gel Electrophoresis and Microsequencing, FASEB Journal, 5, 2200-2208 (1991) (hereinafter "the Celis article") (copy annexed at Tab D);

(e) Franzen, B., Linder, S., Okuzawa, K., Kato, H., Auer, G., Nonenzymatic Extraction of Cells from Clinical Tumor Material for Analysis of Gene Expression by Two-Dimensional Polyacrylamide Gel Electrophoresis, Electrophoresis, 14, 1045-1053 (1993) (hereinafter "the Franzen article") (copy annexed at Tab E);

(f) Bjellqvist, B., Basse, B., Olsen, E., Celis, J.E., Reference Points for Comparisons of Two-Dimensional Maps of Proteins from Different Human Cell Types Defined in a pH Scale Where Isoelectric Points Correlate with Polypeptide Compositions,

Electrophoresis, 15, 529-539 (1994) (hereinafter "the Bjellqvist article") (copy annexed at Tab F); and

(g) Large Scale Biology Company Info; LSB and LSP Information; from http://www.lsbc.com (2001) (copy annexed at Tab G).

8. Many of the published articles I considered (i.e., at least items (a)-(f) identified in paragraph 7) relate to the development of protein two-dimensional gel electrophoretic techniques for use in gene expression monitoring applications in drug development and toxicology. As I will discuss below, a person skilled in the art who read the Hillman '579 application on May 7, 1998 would have understood that application to disclose the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds to be useful for a number of gene and protein expression monitoring applications, e.g., in the use of two-dimensional polyacrylamide gel electrophoresis and western blot analysis of tissue samples in drug development and in toxicity testing.

9. Turning more specifically to the Hillman '579 specification, the SEQ ID NO:1 polypeptide is shown at pages 61-63 as one of five sequences under the heading "Sequence Listing." The Hillman '579 specification specifically teaches that the "the invention further includes a purified antibody which binds to a polypeptide comprising the sequence of SEQ ID NO:1..." (Hillman '579 application at p. 4, lines 17-18). It further teaches that (a) the identity of the SEQ ID NO:1 polypeptide to which the claimed antibody binds was determined from a human "uterus cDNA library (UTRSNOT02)", (b) the SEQ ID NO:1 polypeptide is the growth-associated protease inhibitor chain precursor referred to as "GAPIP" and is encoded by SEQ ID NO:2, and (c) northern analysis shows that GAPIP is expressed in cancer, immune, reproductive, gastrointestinal, nervous and fetal tissues and, therefore, "GAPIP appears to play a role in reproductive, developmental, neoplastic, and immunological disorders" (Hillman '579 application at p. 16, lines 16-22; p. 17, lines 24-27; and p. 28, lines 12-14).

The Hillman '579 application discusses a number of uses of the claimed antibody and SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds in addition to their use in gene expression monitoring applications. I have not fully evaluated these additional

uses in connection with the preparation of this Declaration and do not express any views in this Declaration regarding whether or not the Hillman '579 application discloses these additional uses to be substantial, specific and credible real-world utilities of the claimed antibody and the SEQ ID NO:1 polypeptide to which the antibody specifically binds. Consequently, my discussion in this Declaration concerning the Hillman '579 application focuses on the portions of the application that relate to the use of the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds in gene and protein expression monitoring applications.

10. The Hillman '579 application discloses that the polynucleotide sequences disclosed therein, including the polynucleotides encoding the SEQ ID NO:1 polypeptide, are useful as probes in chip based technologies. It further teaches that the chip based technologies can be used "for the detection and/or quantification of nucleic acid or protein" (Hillman '579 application at p. 25, lines 21-24).

The Hillman '579 application also discloses that the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds are useful in other protein expression detection technologies. The Hillman '579 application states that "[i]mmunological methods for detecting and measuring the expression of GAPIP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS)." (Hillman '579 application at p. 25, lines 25-28). Furthermore, the Hillman '579 application discloses that "[a] variety of protocols for measuring GAPIP, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of GAPIP expression. Normal or standard values for GAPIP expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to GAPIP under conditions suitable for complex formation" (Hillman '579 application at p. 39, lines 21-25).

In addition, at the time of filing the Hillman '579 application, it was well known in the art that "gene" and protein expression analyses also included two-dimensional polyacrylamide gel electrophoresis (2-D PAGE) technologies, which were developed during the

1980s, and as exemplified by the Anderson 1991 and 1995 articles (Tab A and Tab B). The Anderson 1991 article teaches that a 2-D PAGE map has been used to connect and compare hundreds of 2-D gels of rat liver samples from a variety of studies including regulation of protein expression by various drugs and toxic agents (Tab A at p. 907). The Anderson 1991 article teaches an empirically-determined standard curve fitted to a series of identified proteins based upon amino acid chain length (Tab A at p. 911) and how that standard curve can be used in protein expression analysis. The Anderson 1991 article teaches that "there is a long-term need for a comprehensive database of liver proteins" (Tab A at p. 912).

The Wilkins article is one of a number of documents that were published prior to the May 7, 1998 filing date of the Hillman '579 application that describes the use of the 2-D PAGE technology in a wide range of gene and protein expression monitoring applications, including monitoring and analyzing protein expression patterns in human cancer, human serum plasma proteins, and in rodent liver following exposure to toxins. In view of the Hillman '579 application, the Wilkins article, and other related pre-May 7, 1998 publications, persons skilled in the art on May 7, 1998 clearly would have understood the Hillman '579 application to disclose the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity, as explained more fully in paragraph 12 below.

With specific reference to toxicity evaluations, those of skill in the art who were working on drug development in May, 1998 (and for many years prior to May, 1998) without any doubt appreciated that the toxicity (or lack of toxicity) of any proposed drug they were working on was one of the most important criteria to be considered and evaluated in connection with the development of the drug. They would have understood at that time that good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets. Ascertaining that a candidate drug affects its intended target, and identification of undesirable secondary effects (i.e., toxic side effects), had been for many years among the main challenges in developing new drugs. The ability to determine which genes are positively affected by a given drug, coupled with the ability to quickly and at the earliest time possible in the drug development process identify drugs that are likely to be toxic because of their undesirable secondary effects, have enormous value in improving the efficiency of the drug discovery process, and are an important and essential part of

the development of any new drug. In fact, the desire to identify and understand toxicological effects using the experimental assays described above led Dr. Leigh Anderson to found the Large Scale Biology Corporation in 1985, in order to pursue commercial development of the 2-D electrophoretic protein mapping technology he had developed. In addition, the company focused on toxicological effects on the proteome as clearly demonstrated by its goals and by its senior management credentials described in company documents (see Tab G at pp. 1, 3, and 5). Accordingly, the teachings in the Hillman '579 application, in particular regarding use of claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds in differential gene and protein expression analysis (2-D PAGE maps) and in the development and the monitoring of the activities of drugs, clearly includes toxicity studies and persons skilled in the art who read the Hillman '579 application on May 7, 1998 would have understood that to be so.

11. As previously discussed (supra, paragraphs 7 and 8), my experience with protein analysis methods in the mid-1980s and the several publications annexed to this Declaration at Tabs A through F evidence information that was available to the public regarding two-dimensional polyacrylamide gel electrophoresis technology and its uses in drug discovery and toxicology testing before the May 7, 1998 filing date of the Hillman '579 application. In particular the Celis article stated that "protein databases are expected to foster a variety of biological information.... -- among others, ..... drug development and testing" (See Tab D, p. 2200, second column). The Franzen article shows that 2-D PAGE maps were used to identify proteins in clinical tumor material (See Tab E). The Hillman '579 application clearly discloses that expression of GAPIP is associated with cancer, immune, reproductive, gastrointestinal, nervous and fetal tissues (Hillman '579 application at p. 17, lines 24-27 and p.28, lines 12-14). The Bjellqvist article showed that a protein may be identified accurately by its positional co-ordinates, namely molecular mass and isoelectric point (See Tab F). The Hillman '579 application clearly disclosed SEQ ID NO:1 from which it would have been routine for one of skill in the art to predict both the molecular mass and the isoelectric point of the SEQ ID NO:1 polypeptide using algorithms well known in the art at the time of filing.

12. A person skilled in the art on May 7, 1998, who read the Hillman '579 application, would understand that application to disclose the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds to be highly useful in analysis of differential expression of proteins. For example, the specification of the Hillman '579 application would have led a person skilled in the art in May, 1998 who was using protein expression monitoring in

connection with working on developing new drugs for the treatment of reproductive, developmental, neoplastic, and immunological disorders to conclude that a 2-D PAGE map that used the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds would be a highly useful tool and to request specifically that any 2-D PAGE map that was being used for such purposes utilize the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds. Expressed proteins are useful for 2-D PAGE analysis in toxicology expression studies for a variety of reasons, particularly for purposes relating to providing controls for the 2-D PAGE analysis, and for identifying sequence or post-translational variants of the expressed sequences in response to exogenous compounds. Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating reproductive, developmental, neoplastic, and immunological disorders for such purposes as evaluating their efficacy and toxicity.

I discuss in more detail in items (a)-(b) below a number of reasons why a person skilled in the art, who read the Hillman '579 specification in May, 1998, would have concluded based on that specification and the state of the art at that time, that the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds would be highly useful tools for analysis of a 2-D PAGE map for evaluating the efficacy and toxicity of proposed drugs for reproductive, developmental, neoplastic, and immunological disorders by means of 2-D PAGE maps, as well as for other evaluations:

(a) The Hillman '579 application contains a number of teachings that would lead persons skilled in the art on May 7, 1998 to conclude that a 2-D PAGE map that utilized the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds would be a more useful tool for gene expression monitoring applications relating to drugs for treating reproductive, developmental, neoplastic, and immunological disorders than a 2-D PAGE map that did not use the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds. Among other things, the Hillman '579 application teaches that (i) the identity of the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds was determined from a human "uterus cDNA library (UTRSNOT02)," (ii) the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds is the growth-associated protease inhibitor chain precursor referred to as GAPIP, and (iii) GAPIP is expressed in various libraries derived from cancer, immune, reproductive, gastrointestinal, nervous and fetal tissues

and, therefore, "GAPIP appears to play a role in reproductive, developmental, neoplastic, and immunological disorders" (Hillman '579 application at pp. 3, 16 and 28; see paragraph 9, supra). The substantially purified polypeptide could therefore be used as a control to more accurately gauge the expression of GAPIP in the sample and consequently more accurately gauge the affect of a toxicant on expression of the gene. Moreover, GAPIP has chemical and structural similarity with human pre-inter-α-trypsin inhibitor (GI 33985; SEQ ID NO:3), human pre-inter-α-trypsin inhibitor heavy chain H1 (GI 33989; SEQ ID NO:4), and human pre-inter-α-trypsin inhibitor heavy chain H3 (GI 288563; SEQ ID NO:5):

In particular, GAPIP and human pre-inter-α-trypsin inhibitor share 28% identity, one potential N-glycosylation site, four potential casein kinase II phosphorylation sites, four potential protein kinase C phosphorylation sites, the potential signal peptide sequence, and the vWFA3 potential metal-binding site glycine-amino acid-serine-amino acid-serine. In addition, GAPIP and human pre-inter-α-trypsin inhibitor heavy chains H1 and H3 share 27% and 23 % identity, respectively, one potential N-glycosylation site, four potential casein kinase II phosphorylation sites, five potential protein kinase C phosphorylation sites, the potential signal peptide sequence, and the vWFA3 potential metal-binding site glycine-amino acid-serine-amino acid-serine. As illustrated by Figure 3, GAPIP and human pre-inter-α-trypsin inhibitor heavy chains share a common phylogenic heritage. A fragment of SEQ ID NO:2 from about nucleotide 982 to about nucleotide 1011 is useful, for example, for designing oligonucleotides or as a hybridization probe. Northern analysis shows the expression of this sequence in various libraries, at least 63% of which are immortalized or cancerous and at least 26% of which involve immune response. Of particular note is the expression of GAPIP in reproductive, gastrointestinal, nervous, and fetal tissues. (Hillman '579 application at p. 17, lines 9-21)

(b) Persons skilled in the art on May 7, 1998 would have appreciated (i) that the protein expression monitoring results obtained using a 2-D PAGE map that utilized the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds would vary, depending on the particular drug being evaluated, and (ii) that such varying results would occur both with respect to the results obtained from the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds and from the 2-D PAGE map as a whole (including all its other individual proteins). These kinds of varying results, depending on the identity of the drug being tested, in no way detracts from my conclusion that persons skilled in the art on May 7, 1998, having read the Hillman '579 application specification, would specifically request that any 2-D PAGE map that was being used for conducting protein

expression monitoring studies on drugs for treating reproductive, developmental, neoplastic, and immunological disorders (e.g., a toxicology study or any efficacy study of the type that typically takes place in connection with the development of a drug) utilize the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds. Persons skilled in the art on May 7, 1998 would have wanted their 2-D PAGE map to utilize the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds because a 2-D PAGE map that utilized such protein sequence information (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using 2-D PAGE maps that persons skilled in the art have been doing since well prior to May 7, 1998. The foregoing is not intended to be an all-inclusive explanation of all my reasons for reaching the conclusions stated in this paragraph 12, and in paragraph 6, supra. In my view, however, it provides more than sufficient reasons to justify my conclusions stated in paragraph 6 of this Declaration regarding the Hillman '579 application disclosing to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds.

13. Also pertinent to my considerations underlying this Declaration is the fact that the Hillman '579 application disclosure regarding the uses of the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds for protein expression monitoring applications is not limited to the use of that protein in 2-D PAGE maps. For one thing, the Hillman '579 application disclosure regarding the technique used in gene and protein expression monitoring applications is broad (Hillman '579 application at, e.g., p. 25, lines 19-28 and p. 39, lines 21-25).

In addition, the Hillman '579 application repeatedly teaches that the protein described therein (including the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds) may desirably be used in any of a number of long established "standard" techniques, such as ELISA or western blot analysis, for conducting protein expression monitoring studies. See, e.g.:

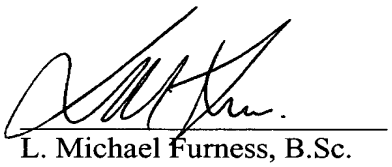
(a) Hillman '579 application at p. 25, lines 25-28 ("Immunological methods for detecting and measuring the expression of GAPIP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS)");

(b) Hillman '579 application at p. 39, lines 21-25 ("A variety of protocols for measuring GAPIP, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of GAPIP expression. Normal or standard values for GAPIP expression are established by combining body fluids or cell extracts taken from normal

mammalian subjects, preferably human, with antibody to GAPIP under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, preferably by photometric means. Quantities of GAPIP expressed in subject samples, control and disease, from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.").

Thus a person skilled in the art on May 7, 1998, who read the Hillman '579 specification, would have routinely and readily appreciated that the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds disclosed therein would be useful to conduct gene expression monitoring analyses using 2-D PAGE mapping or western blot analysis or any of the other traditional membrane-based protein expression monitoring techniques that were known and in common use many years prior to the filing of the Hillman '579 application. For example, a person skilled in the art in May 1998 would have routinely and readily appreciated that the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds would be a useful tool in conducting protein expression analyses, using the 2-D PAGE mapping or western analysis techniques, in furtherance of (a) the development of drugs for the treatment of reproductive, developmental, neoplastic, and immunological disorders, and (b) analyses of the efficacy and toxicity of such drugs.

14. I declare further that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, and that willful false statements may jeopardize the validity of this application and any patent issuing thereon.



L. Michael Furness, B.Sc.

Signed at Cambridge, UK
This 18th day of October, 2002